

FORM PTO-1449		US Dept. of Commerce Patent and Trademark Office		ATTORNEY DOCKET NO. 4012-113 DIV1		SERIAL NO. 09/429,798	
INFORMATION DISCLOSURE STATEMENT (use several sheets if necessary)				APPLICANT Ekwuribe et al.			
				FILING DATE October 29, 1999		GROUP	

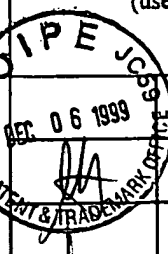

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL	PATENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE	
[Handwritten marks]	AA	4,585,754	29 Apr. 1986	Meisner et al.			
	AB	4,179,337	18 Dec. 1979	Davis et al.			
	AC	4,003,792	18 Jan. 1977	Mill et al.			
	AD	4,849,405	18 Jul. 1989	Ecanow			
	AE	5,013,556	7 May 1991	Woodle et al.			
	AF	4,963,367	16 Oct. 1990	Ecanow			
	AG	4,044,196	23 Aug. 1977	Hüper et al.			
	AH	4,717,566	5 Jan. 1988	Eckenhoff et al.			
	AI	4,698,264	6 Oct. 1987	Steinke			
	AJ	4,684,524	4 Aug. 1987	Eckenhoff et al.			
	AK	4,410,547	18 Oct. 1983	Ueno et al.			
	AL	3,256,153	14 Jun. 1966	Heimlich			
	AM	4,935,246	19 Jun. 1990	Ahrens			
	AN	4,797,288	10 Jan 1989	Sharma et al.			
	AO	4,744,976	17 May 1988	Snipes et al.			
	AP	5,055,304	8 Oct. 1991	Makino et al.			
	AQ	5,055,300	8 Oct. 1991	Gupta			
	AR	4,772,471	20 Sep. 1988	Vanlerberghe et al.			
	AS	5,093,198	3 Mar. 1992	Speaker et al.			
	AT	4,840,799	20 Jun. 1989	Appelgren et al.			
AU	4,622,392	11 Nov. 1986	Hong et al.				
AV	5,653,987	5 Aug. 1997	Modi et al.				
AW	5,792,834	11 Aug. 1998	Hakimi et al.				
AX	5,595,732	21 Jan. 1997	Hakimi et al.				
AY	5,539,063	23 Jul. 1996	Hakimi et al.				

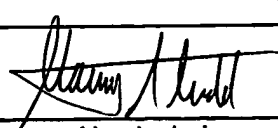
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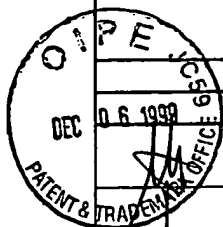
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FORM PTO-1449		US Dept. of Commerce Patent and Trademark Office		ATTORNEY DOCKET NO. 4012-113 DIV1		SERIAL NO. MAY 01 2000 09/429,798	
INFORMATION DISCLOSURE STATEMENT (use several sheets if necessary)				APPLICANT Ekwuribe et al.		TECHNICAL CENTER 1600/2900 DEC 06 1999 U.S. PATENT & TRADEMARK OFFICE	
				FILING DATE October 29, 1999			
EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AZ	5,559,213	24 Sep 1996	Hakimi et al.			
	BA	5,747,646	5 May 1998	Hakimi et al.			
	BB	5,286,637	15 Feb. 1994	Veronese et al.			
	BC	5,631,263	20 May 1997	Portoghese et al.			
	BD	5,602,099	11 Feb. 1997	Schiller			
	BE	5,545,719	13 Aug. 1996	Shashoua et al.			
	BF	5,641,861	24 Jun. 1997	Dooley et al.			
	BG	5,663,295	2 Sep. 1997	Moreau et al.			
	BH	5,786,447	28 Jul. 1998	Schiller et al.			
	BI	4,939,174	3 Jul. 1990	Shashoua			
	BJ	5,932,462	Aug. 3, 1999	Harris et al.			
FOREIGN PATENT DOCUMENTS							
		DOCUMENT NUMBER	PUBLICATION DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO
							X
OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.)							
	BK	Alyautdin, R.N., "Delivery of Loperamide Across the Blood-Brain Barrier with Polysorbate 80-Coated Polybutylcyanoacrylate Nanoparticles," Pharm. Res. J., 1997, 14: 325-328.					
	BL	Aoshima, M. et al., "N ⁴ -Behenoyl-1-β-D-Arabinofuranosylcytosine as a Potential New Antitumor Agent," Cancer Research, 1977, 37: 2481-2486.					
	BM	Banting, R. G., et al., "Pancreatic Extracts in the Treatment of Diabetes Mellitus," The Canadian Med. Assoc. J. 1922, 12: 141-146.					
	BN	Baker, D. C. et al., "Prodrugs of 9-β-D-Arabinofuranosyladenine. 1. Synthesis and Evaluation of Some 5'-(O-Acyl) Derivatives," J. Med. Chem., 1978, 21(12): 1218-1221.					
	BO	Banks, W.A., et al., "Passage of Peptides Across the Blood-Brain Barrier: Pathophysiological Perspectives," Life Sciences, 1996, 59 (23), 1923-1943.					
	BP	Boccu, E. et al., "Pharmacokinetic Properties of Polyethylene Glycol Derivatized Superoxide Dismutase," Pharm. Res. Comm., 1982, 14: 11-120.					
	BQ	Bodor, N., et al., "A Strategy for Delivering Peptides into the Central Nervous System by Sequential Metabolism," Science, 1992, 257, 1698-1702.					
Continued on page 3							
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	BR	Bodor, N., et al., "Molecular Packaging. Peptide Delivery to the Central Nervous System by Sequential Metabolism," Amer. Chem. Soc., 1995: 317-337.					
	BS	Brange, J. et al., "Chemical Stability of Insulin. 1. Hydrolytic Degradation During Storage of Pharmaceutical Preparations," Pharm. Res., 1992, 9 (6): 715-726.					
	BT	Brange, J. et al., "Chemical Stability of Insulin. 2. Formation of Higher Molecular Weight Transformation Products During Storage of Pharmaceutical Preparations," Pharm. Res., 1992, 9 (6): 727-734.					
	BU	Brewster, M.E., et al., "Effect of Molecular Manipulation on the Estrogenic Activity of a Brain-Targeting Estradiol Chemical Delivery System," J. Med. Chem., 1994, 37: 4237-4244					
	BV	Brewster, M.E., et al., "Efficacy of a 3-Substituted Versus 17-Substituted Chemical Delivery System for Estradiol Brain Targeting," J. Pharm. Sci., 1994: A-E.					
	BW	Brewster, M., et al., "Tissue Distribution of LY231617, an Antioxidant with Neuroprotectant Activity, in the Rat," J. Pharm. Studies, 1995, 84 (7): 791-793.					
	BX	Conradi, R.A., et al., "The Influence of Peptide Structure on Transport Across Caco-2 Cells," Pharm. Res., 1991, 8 (12): 1453-1459.					
	BY	Chen, C., et al., "Extensive Biliary Excretion of the Model Opioid Peptide [D-PEN ^{2,5}] Enkephalin in Rats," Pharm. Res. J., 14: 345-350.					
	BZ	Chiou, G.C.Y., et al., "Systemic Delivery of Enkephalin Peptide through Eyes," Life Sciences, 1988, 43: 509-514.					
	CA	Chun, W., et al., "Transmucosal Delivery of Methionine Enkephalin. I: Solution Stability and Kinetics of Degradation in Various Rabbit Mucosa Extracts," J. Pharm.Sci., 1993, 82 (4): 373-378.					
	CB	Fix, J.A., "Oral Controlled Release Technology for Peptides: Status and Future Prospects," Pharm. Res., 1996, 13 (12): 1760-1763.					
	CC	Gibson, A.M., et al., "Specificity of Action of Human Brain Alanyl Aminopeptidase on Leu-Enkephalin and Dynorphin-Related Peptides," Neuropeptides, 1989, 13: 259-262.					
	CD	Gish, D. T. et al., "Nucleic Acids. 11. Synthesis of 5'-Esters of 1-β-D-Arabinofuranosylcytosine Possessing Antileukemic and Immunosuppressive Activity," J. Med. Chem., 1971, 14(12): 1159-1162.					
	CE	Hong, C. I. et al., "Nucleoside Conjugates. 7. Synthesis and Antitumor Activity of 1-β-D-Arabinofuranosylcytosine Conjugates of Ether Lipids," J. Med. Chem., 1986, 29: 2038-2044.					
	CF	Horvat, J., et al., "Synthesis and Biological Activity of [Leu ⁵] Enkephalin Derivatives Containing D-Glucose," J. Peptide Protein Res., 1988, 31: 499-507.					
	CG	Hostetler, K. Y. et al., "Synthesis and Antiretroviral Activity of Phospholipid Analogs of Azidothymidine and Other Antiviral Nucleosides," The Journal of Biological Chemistry, 1990, 265(11): 6112-6117.					
	CH	Kroll, R.A., et al., "Outwitting the Blood-Brain Barrier for Therapeutic Purposes: Osmotic Opening and Other Means," 1998 Neurosurgery, 42 (5): 1083-1100.					
	CI	Maislos, M. et al., "The Source of the Circulating Aggregate of Insulin in Type I Diabetic Patients is Therapeutic Insulin," J. Clin. Invest., 1986, 77: 717-723.					
	CJ	Mosnaim, A.D., et al., "Studies of the in Vitro Human Plasma Degradation of Methionine-Enkephalin," Gen. Pharmac., 1988, 19 (5): 729-733.					
	CK	Nestor, J., "Improved Duration of Action of Peptide Drugs," Amer. Chem Soc. 1995: 449-471.					
CL	Oka, K. et al., "Enhanced Intestinal Absorption of a Hydrophobic Polymer-Conjugated Protein Drug, Smancs, in an Oily Formulation," Pharm. Res., 1990, 7 (8): 852-855.						
Continue on Page 4							
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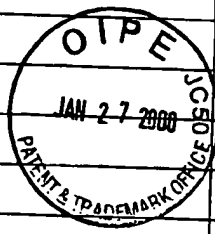
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OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.)							
	CM	Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995: 265-296.					
	CN	Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792.					
	CO	Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245.					
	CP	Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24).					
	CQ	Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39: 728-733.					
	CR	Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841.					
	CS	Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084.					
	CT	Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608.					
	CU	Shashoua V.E., et al., "γ-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664.					
	CV	Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354.					
	CW	Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[γ ³⁵ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246.					
	CX	Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316.					
	CY	Tsuzuki, N., et al., "Rapid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala ²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8.					
	CZ	Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529.					
	DA	Weber, S.J., et al., "Distribution and Analgesia of [³ H][D-PEN ² , D-PEN ⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112.					
	DB	Weber, S.J., et al., "Whole Body and Brain Distribution of [³ H]Cyclic [D-PEN ² , D-PEN ⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316.					
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FORM PTO-1449 US Dept. of Commerce Patent and Trademark Office SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (use several sheets if necessary)	ATTORNEY DOCKET NO.	SERIAL NO.
	4012-113 DIV1	09/429,798
	APPLICANT	
	Ekwuribe et al.	
	FILING DATE	GROUP
	October 29, 1999	1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	PATENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE



FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	PUBLICATION DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	NO
<i>AA</i>	WO 93/01802	Feb 4, 93	PCT				X

OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.)

AB Delgado et al. "The Uses and Properties of PEG-Linked Proteins". *Critical Review in Therapeutic Drug Carrier Systems*, 9(3, 4):249-304 (1992).

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Patent and Trademark Office

Attorney Docket Number
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LIST OF DOCUMENTS CITED BY APPLICANT

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Applicants:

Ekwuribe et al.

Filing Date:
October 29, 1999

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1627

U. S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
<i>JA</i>	1.	5,681,811	10/28/97	Ekwuribe	514	8	
<i>JA</i>	2.	5,693,769	12/02/97	Kahne et al.	536	5	

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FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

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